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MINOR FAT-SOLUBLE FACTORS IN NUTRITION

By RUTH WOODS

Dietary fats serve, among other things, as carriers of important fat soluble nutritive essentials of which the best known are the vitamins. These may be arbitrarily divided into two groups, the major one including the well-known fat soluble vitamins—vitamin A, vitamin D, vitamin E and vitamin K. Most of these have already been discussed in previous issues.* The second group includes a number of less well-known vitamins or vitamin-like factors, namely the so-called essential unsaturated fatty acids,* an anti-stiffness factor for guinea pigs in raw cream, a hypothetical growth factor in butterfat, and vaccenic acid, a postulated growth factor said to be present in *summer* butter and, in modified form, in China wood oil. The present paper will review the status and significance of the two latter factors.

Growth Factor in Butter:

Early History: During a series of animal nutrition studies begun in 1938 at the University of Wisconsin, it was noticed that very young animals grew somewhat faster and appeared to have better coats of hair when fed a basic skim milk diet supplemented with butterfat than when fed the same diet with vegetable fats and the necessary vitamins to compensate for those occuring naturally in butterfat (1). Preliminary results of investigations into the reason for the difference were reported two years later. At that time, Schantz, Elvehjem and Hart (2) reported that various skim milk samples fortified with essential minerals (iron, copper, manganese) and to which different fats had been added all produced good growth. However, mineralized skim milk with added corn oil, coconut oil, cottonseed oil or soybean oil in place of the natural butterfat, did not stimulate as good growth especially during the early weeks of life. After considerable investigation of the activity of the various fractions of butterfat, these workers demonstrated that the growth promoting activity was localized in the saponifiable (true fat) portion.

A first possibility appeared to be that the growth stimulating activity might be due to some particular phospholipid in the butterfat. Accordingly, tests were conducted in which a common phospholipid, egg lecithin, was added to the vegetable oils in amounts calculated to render the phospholipid

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**cf. Borden's Review of Nutrition Research,* April, 1943—"The Story of Vitamin K." December, 1943—"Nutrition and Vision: Vitamin A." June, 1945—"Experimental Vitamin E Deficiency." September, 1945—"Vitamin E in Veterinary and Clinical Medicine." April, 1948—"The Essential Fatty Acids."

content of these oils equivalent to that of butter (3). Results showed that egg lecithin improved the nutritive value of corn oil and coconut oil slightly, but not enough to give growth equal to that obtained on butterfat. Other phospholipids were ineffective as supplements to the vegetable oils. The additional fact that soybean oil was found to be less active than butterfat despite its high phospholipid content, offered further indication that the unidentified growth factor was something other than a phospholipid in the saponifiable fraction of butter.

The Active Fraction: This narrowed down the search for the growth factor to the fatty acids in butter. These were separated into three fractions: The volatile acids; the non-volatile saturated acids; and the non-volatile unsaturated acids. Each of these fractions was incorporated separately into a vegetable oil and the three samples compared as to growth promoting effects. It was found that the vegetable oil containing the *saturated* fatty acid fraction of the butterfat was the only one which effectively promoted superior growth (4). This led to the conclusion that the growth stimulating activity was caused by one or more of the *saturated* fatty acids in butter.

Effect of Hydrogenation (on Butterfat): As a check against the possibility that the activity of the saturated fatty acid fraction actually might be due to the presence of an *unsaturated acid* accidentally remaining as an impurity, Boutwell *et al* (5) subjected the active saturated fraction to complete hydrogenation. Tests with the completely hydrogenated saturated fraction confirmed the original hypothesis. As a further extension of their studies, Boutwell's group also subjected the inactive unsaturated fatty acid fraction of butter to hydrogenation and found it then to be even superior to the original active fraction. This led them to postulate that butterfat possesses a growth stimulating factor existing in two forms: An active form, probably a long-chain saturated fatty acid (or acids), and an inactive precursor in unsaturated form which may be converted to the active factor by hydrogenation. They postulated further that it was this unknown factor which was responsible for the superior growth promoting activity of butterfat in rats during the first three weeks of life.

Effect of Hydrogenation (on Vegetable Fats): In view of the increased growth obtained on the hydrogenated butterfat fractions, feeding experiments were also carried out on various hydrogenated vegetable oils. It was found that hydrogenation failed to improve the nutritive value of these oils and it was concluded that the vegetable oils tested (corn oil, coconut oil, cottonseed oil and soybean oil) do not possess the unsaturated precursor of the unknown growth factor.

Effect of Lactose: Two years later, Boutwell, Geyer, Elvehjem and Hart (6) reported the additional interesting fact that the nature of the carbohydrate in the basal skim milk ration apparently had a definite effect on the nutritive value of the supplementary fat. They found that when lactose was the sole carbohydrate provided, butterfat was superior to vegetable oils in growth promoting properties. When, however, mixed carbohydrates were used such as usually appear in the ordinary human diet (sucrose, dextrose, starch or dextrin), the superiority of butterfat disappeared and in some cases, growth on vegetable oils was better. Several theories (6, 7) were advanced to explain these differences. One of these postulated that utilization of lactose was less efficient than that of mixed carbohydrates, thus rendering less carbohydrate available for conversion to fat. Another theory suggested that lactose, as compared with the other carbohydrates, in some way affects the vitamin-synthesizing activity of the intestinal flora and that butterfat counteracts this effect either by supplying an essential growth factor or by stimulating the intestinal flora to produce some unknown essential.

Findings of Other Workers:

Shortly after the preliminary papers of Schantz *et al* (2, 3, 4) the presence of a new growth factor in butter was confirmed by the Danish workers, Boer and Jansen (8, 9). Their results differed in several essential aspects from those of the American workers. At that time, however, no explanation for the discrepancies could be found (see p. 6, "Vaccenic Acid"). The value of butterfat for young calves was next reported by Gullickson *et al* (10). Opposing these findings were those of Euler *et al* (11) in Sweden, who reported better growth of rats on margarine diets as compared with butter. Contrary to this, Harris and Mosher (12) reported more rapid growth of weanling rats on butter and of older rats on coconut oil. Freeman and Ivy (13) found no statistically significant differences in growth of young rats on butter or vegetable fat diets until after three months when the butterfat rats showed significant gains.

Detailed investigation of this somewhat confused field of study was begun in 1943 by Deuel and associates in California. Their findings conflicted sharply with those of the Wisconsin group and for several years following numerous attempts have been made to find a satisfactory explanation for the discrepancies in results reported by these two research groups. Following is a brief resumé of the more interesting aspects of this as yet unsolved controversy.

A preliminary study by Deuel, Movitt and Hallman (14) revealed no

differences in growth of young rats on either butterfat, vegetable oils (corn, cottonseed, olive, peanut, soybean) or a vegetable margarine, even with lactose as the only carbohydrate. In one instance only a slight superiority of butterfat was observed in female rats after 12 weeks on the butter diet. This difference was considered too small to be statistically significant and disappeared entirely in a subsequent experiment in which diacetyl (butter flavor) was added to the vegetable fats. Deuel *et al* found that young rats prefer butter flavor and will eat more of butter or of butter-flavored vegetable oils than of non-flavored oils. They suggested that the superior growth obtained with butterfat by Schantz and Elvehjem (2) was probably the result of a greater food consumption by the rats on the butter diet due to preference for butter flavor. In subsequent reports, Deuel *et al* (15, 16) cited the following points in an attempt to explain further the differences between their findings and those of the Wisconsin group:

1. Possible variations between the two groups with respect to distribution or "spread" of litters, inequality in weights of animals in various groups, differences in uniformity of diets, and possibility of rancidity factors altering the nutritional quality of the diet.

2. Only carotene was used by Schantz *et al* as the source of vitamin A with the vegetable fats whereas some vitamin A, as such, must have been received by the animals eating butter. Deuel *et al* fed all of their animals vitamin A. They suggested that possible inefficient utilization of carotene put the animals on that supplement at a disadvantage. However, if the supply of carotene was very liberal, sufficient vitamin was available and the difference in the two sets of experiments becomes insignificant.

3. The *ad libitum* feeding method used by Schantz *et al* resulted in a greater consumption of butter in preference to the vegetable fats. In Deuel's experiments the consumption of all the fats was approximately the same.

   As a rebuttal to the argument that their rats ate more butter because they preferred butter flavor, Boutwell *et al* (17) fed butter from which the diacetyl had been removed and corn oil to which diacetyl had been added. They confirmed their original findings with respect to butter. Boutwell's group stated further, *"paired feeding penalizes the superior food and ultimately obliterates the difference as measured by the growth rate and well-being of the experimental animal."* They stated also that *"on purified diets the true explanation for the superior growth promoting value of one substance over another must lie in the existence of specific compounds in that superior nutrient which results in a more favorable physiological response such that the animal grows at a faster rate and hence consumes more ration."*

   This, in turn, was taken up in counter-rebuttal by Deuel *et al* (18). They maintained that flavor preference and not increased growth rate was responsible for the greater consumption of butter over vegetable fats. As a further proof of this theory they administered growth hormone to animals on butter and various vegetable fat diets, stating that *"it is our opinion that an excellent method to*

test the nutritional value of a diet is by its ability to support the additional growth occasioned by the injection of growth hormone."
They found that when growth hormone was injected, the augmented growth was as great or greater with the rats receiving the vegetable fat diets as with those receiving butterfat. Since deficient diets had been shown to be unable to support the extra growth induced by growth hormone (19), Deuel *et al* concluded that this experiment is indicative of the fact that the various vegetable fats and oils have an ability equal to butter in supporting added growth requirements.

4. Another point of interest was the suggestion (20) that the failure of Deuel's group to observe differences between butter and vegetable fat diets might be due to the fact that they used unextracted skim milk powder containing a small amount of residual butterfat and were thus, inadvertently supplying their vegetable fat animals with butterfat, too. In reply to this Deuel *et al* (21) raised four points:

   a. In the original work of Schantz, Elvehjem and Hart (2) unextracted liquid skim milk was used and the greatest differences between the two groups of fats observed.

   b. In subsequent studies by the Wisconsin group, extracted skim milk powder was used but the extraction method was reported by Deuel's group to result in a residual butterfat content almost equal to that of non-extracted milk.

   c. The amount of residual fat available to the rat from unextracted skim milk powder was calculated by Deuel *et al* to be about 77 mg. per day. Of this amount, only 28 mg. are saturated fatty acids (the active fraction as designated by Schantz *et al)*. This fraction consists largely of palmitic and stearic acids, so that only a very minute quantity of any unidentified fatty acid is left in such a skim milk powder. This may, however, merely mean that the hypothetical fatty acid is extremely potent and effective in few milligram quantities.

   d. Repetition of the work of Deuel *et al* using extracted skim milk (with traces of residual butterfat) failed to alter their original results.

Numerous other reports by various groups of workers have appeared on all phases of this interesting subject but it is impossible to include these within the limitations of this Review. A summary of the findings reveals only a very confused picture with much to be said on both sides. Some workers have confirmed the apparent superior growth promoting value of butter; others have demonstrated better growth with vegetable oils and margarines; still others have shown that, aside from vitamin content, no apparent nutritional difference exists between these two classes of fats. As Cowgill (22) has pointed out in his comprehensive summary of the early work in this field, "it seems evident that only further work on this problem by different groups of workers using the same rations, strains of animals, and as nearly the same experimental condition as is possible *(as well as*

similar and careful statistical evaluation of their findings)* can resolve this interesting controversy.

Vaccenic Acid:

The existence of a new fat soluble nutritional essential was announced some time ago with the statement by Boer *et al* (23) that vaccenic acid is the growth promoting factor in summer butter postulated by them some years ago. It was suggested that vaccenic acid and the unidentified butter growth factor of Schantz *et al* might be the same. There is ample reason, however, to conclude that the two factors are not identical. To further complicate the picture, the work of other investigators has cast considerable doubt as to the assumption that vaccenic acid possesses the nutritional properties claimed for it by the Danish workers.

The story of vaccenic acid began seven years ago with the observation of Boer and Jansen (8, 9) that young rats grew better when fed summer butter in place of olive or peanut oil. The apparent superiority of butter was attributed to an unknown factor after ruling out the possible influence of vitamin A, vitamin D or the essential unsaturated fatty acids (linoleic, linolenic and arachidonic). The failure of Euler and coworkers (11) to reproduce these results (see p. 3) was attributed to the fact that they apparently did not use summer butter (derived from cows on fresh pasture). Boer and Kentie interpreted their findings as confirmation of the original work of Schantz and Elvehjem (2), although certain discrepancies were noted which could not be explained at that time.

Subsequently Boer, Jansen and Kentie (25) reported in considerable detail results of their continued investigations on this newly postulated summer factor. In the first of these experiments eight groups of four week old rats were placed on a common basal diet, each group, however, receiving a different supplement consisting of various fractions of butterfat or of peanut oil, with or without vitamin A (as carotene) and vitamin D (as calciferol). (See Table 1.)

After four weeks on the experiment practically no differences were observed between the weights of the rats on any of the peanut oil diets and those of the rats on any of the corresponding diets containing the fatty acids (esters) of summer butter. *By the end of the tenth week, however, marked differences became apparent (Table 1).** In 18 of the 27 pairs of litter mates, the growth of the rat receiving summer butter esters was better than the

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*Ed. comment.

*Italicized statements in this section indicate findings contradictory to those of Schantz and Elvehjem.

TABLE 1

Growth of rats demonstrating the presence of a growth factor in summer butter.[1]

NUMBER OF RATS	GROUP I	II	III	IV	Groups I, II, III and IV combined.	V	VI	VII	VIII	Group V, VI, VII and VIII combined.
	19	19	16	18		11	16	14	15	
Week										
4	99	99	97	97	98	97	89	89	87	90
5	122	123	119	120		118	111	110	109	
6	145	145	142	141	143	136	127	131	127	130
7	160	155	161	158	158	148	141	145	142	144
8	176	171	172	169	172	163	149	158	150	154
9	186	181	180	177	181	174	158	168	162	165
10	196	190	189	183	190	185	165	177	169	173

[1]Mean weights of rats by groups at the end of each week from the fourth to the tenth week of the experiment. Dietary supplements for the different groups:

Group I. Esters of the fatty acids and unsaponifiable part of summer butter.
Group II. Esters of the fatty acids of summer butter and calciferol plus carotene.
Group III. Esters after adsorption and unsaponifiable part of summer butter.
Group IV. Esters after adsorption and calciferol plus carotene.
Group V. Peanut oil and unsaponifiable part of summer butter.
Group VI. Peanut oil and calciferol plus carotene.
Group VII. Peanut oil after adsorption and unsaponifiable part of summer butter.
Group VIII. Peanut oil after adsorption and calciferol plus carotene.

growth of the litter mate receiving peanut oil. (There was no significant difference in litter mate comparison between the rats receiving the unsaponifiable parts of butter and those receiving calciferol and carotene. Treatment of either fat with fuller's earth had no effect on growth promoting values). The authors comment as follows:

> "The rats were therefore considered as 2 groups: the first group contained all those rats which had received the summer butter acids or esters whether treated or untreated, and the second group contained all the rats which had received peanut oil whether treated by adsorption or not. The data are presented in table 1, where the body weights after 4, 5, 6, 7, 8, 9, and 10 weeks are given. After 10 weeks the mean weight of rats on the esters of the fatty acids of summer butter is 190 gm. (column 6) as compared with a mean weight of rats on peanut oil of 173 gm. (last column). The question arises, whether this difference of 17 gm. in the mean weight of the 2 groups of rats is significant. It must first be considered, whether the sub-groups which have been combined together to make the larger groups comprise homogeneous material, statistically speaking. When the distribution of growth figures within each group is considered, there is no evidence of departure from statistically normal distribution, and therefore we are entitled to

conclude that each group is statistically homogeneous. We are also entitled to compare the means of the 2 groups, and it appears that the difference of 17 gm. is significant, since it is 4.6 times as great as the standard error of the difference between the 2 means. We are therefore justified in concluding that after 10 weeks there is a highly significant difference between the weights of rats receiving summer butter acids as compared with those of rats receiving peanut oil. This difference in weight can only be attributed to the esters of summer butter."

These preliminary studies confirmed the original hypothesis concerning the summer butter factor and hinted at the possibility of a similar factor being present in the non-saponifiable fraction of butter as well. In their next series of experiments, Boer *et al* found an appreciable loss of activity of summer butter after adsorption on fuller's earth or after hydrogenation. *The destruction of the active factor by hydrogenation strongly indicated that the factor was an unsaturated fatty acid.* Fractionation of the fatty acids of butter confirmed this conclusion:

Note: In this third series of experiments, the authors changed from peanut oil to olive oil and rape-seed oil for two reasons. Peanut oil became unavailable during the war, and later so did olive oil; furthermore, growth differences between butterfat and olive or rape-seed oil became apparent much sooner and to a greater extent than when peanut oil was used, thereby shortening the duration of the experimental period required.

In order to account for the discrepancy between their findings and those of Schantz *et al* (2) who indicated that the butter growth factor is a saturated acid, Boer *et al* postulated that their factor "is an unsaturated substance containing 18 C-atoms which, after Twitchell separation, is found in the saturated fatty acid fraction."* They continue, "it is distinct from oleic, linoleic and linolenic acids. The only known acid which satisfies the above conditions is vaccenic acid."

The identification of vaccenic acid as the growth stimulating factor in their active butter fraction was believed to be confirmed by the fact that a fat fraction obtained from China wood oil and consisting largely of vaccenic acid exerted similar growth activity (23). Since it was not possible to obtain completely pure vaccenic acid from either butter or China wood oil, absolute proof of the activity of vaccenic acid, however, could not be claimed.

Contradictory Findings: Although the findings of the Danish workers are clear cut and well substantiated by their experimental data, Deuel *et al* (24) and, more recently, other investigators, have been unable, with one exception, to confirm their finding. The California group concurs in the

*This still conflicts with the findings of the Wisconsin workers who later proved, by hydrogenation studies, that their factor could not be an unsaturated acid remaining in the saturated fraction.

view that rape-seed oil is inferior to butterfat (as well as to the common vegetable fats used in this country). This they attribute largely to the poorer absorption and digestibility of this oil (26). In reproducing the experiments of Boer *et al* (23) Deuel's group used only rape-seed oil. Thus far they have reported no studies on olive oil and offer no explanation for the inferior results obtained by Boer *et al* with olive and peanut oils, both well digested oils.

With respect to the activity of vaccenic acid itself, the California group is again in disagreement with the Danish group. Deuel *et al* (24) found that not only was a highly purified sample of vaccenic acid ineffective, but that it actually exhibited an unexplained depressant effect on growth.

Following these observations, Nath, Barki, Elvehjem and Hart (27) also repeated studies with vaccenic acid. They used both synthetic vaccenic acid and that isolated from natural fats. Their results confirmed the findings of Deuel *et al* (24) that no increase in growth of young rats resulted from the supplementation with vaccenic acid of diets containing corn oil or olive oil. Although their studies confirmed earlier reports by Boutwell *et al* (6, 28) that butterfat is superior to corn oil when lactose is the sole carbohydrate of the diet, they found no effect of vaccenic acid supplementation under these special conditions either. This led them to conclude that, although butter appears to have growth stimulating properties on a lactose diet, this activity cannot be attributed to vaccenic acid.

Nath *et al* cite, further, the work of Jack and Hinshaw (29) on the nutritive value of fractions obtained by cold crystallization of milk fat which indicates that some other factor or factors must be responsible for the observed growth promoting activity of milk fat. Jack and Hinshaw found that one fraction (identified as the—53°C. filtrate fraction) had a growth promoting activity much superior to that of the whole milk fat itself. The existence of such a fraction was also observed in independent studies by Nath and associates (30, 31).

Nath *et al* (27) conclude that "from all these experiments it is obvious that vaccenic acid has no special growth stimulating properties. The fact still remains that there is something present in butterfat at certain seasons of the year which may be either a definite chemical compound or, more likely, a fraction rich in certain favorable fatty acids."

Although, at the present time, most investigators have been unable to demonstrate any growth promoting effect of vaccenic acid, the possibility that another, closely related acid might be responsible for the effects observed by Boer *et al* (25) was investigated very recently by Deuel and coworkers (32). They studied the activity of another unsaturated fatty acid whose

meeting point and other identifying characteristics are almost identical with those for vaccenic acid and which, therefore, might have been confused with vaccenic acid. Detailed experiments, however, revealed that neither vaccenic acid nor this nearly identical compound display any demonstrable growth promoting properties.

Several weeks ago, results of another approach to the problem were reported by Lassen and Bacon (33). They used completely fat-free diets* to which were added small supplements of butter, cottonseed oil, olive oil and a commercial vegetable fat. Each of the supplements was found to produce comparable results with respect to growth stimulating ability, thus demonstrating that none contains a special unidentified factor which is not present in each of the others. Further, since the addition of cottonseed oil, known to be free of vaccenic acid (34) produced the best gain in weight and body length (though not of statistical significance), any special nutritional role of vaccenic acid was thereby ruled out.

Conclusion:

Although the final word in this story may yet be forthcoming, the present status of affairs would seem to indicate only one positive finding, namely that it has been impossible to confirm any growth-promoting activity for vaccenic acid. With respect to the relative nutrition merits of the various types of food fats, a possibility exists that a certain fraction of milk fat may be more growth stimulating than the entire fat itself, although the consensus among nutrition investigators seems to be that the common animal and vegetable fats are just about equal in over-all nutritive value.

*Shown in earlier tests to cause signs of essential fatty acid deficiency.

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